REMARKS

The Office Action of June 9, 2009 has been carefully studied. Favorable reconsideration and allowance of the claims are respectfully requested.

I. Claim Status and Amendments

Claims 4-8, 11, 20, 22-27, and 31-36 presently appear in this application. Claims 11, 20 and 22 have been withdrawn as being drawn to non-elected subject matter. Claims 4-8, 23-27 and 31-36 have been examined on the merits and stand rejected. Claim 26 has also been objected to.

By way of the present amendment, Applicants have amended the claims to a non-narrowing manner to address formal matters raised in the Office Action and to correct inadvertent errors made in the filing of the response filed February 9, 2009. Support can be found in the claims as filed and throughout the disclosure, for example, at paragraphs [0032]-[0035] on pages 16-17. Applicants also made minor editorial revisions to certain claims, where needed, to better conform to US claim form and practice. Such revisions are non-narrowing. For instance, claims 4 and 31 have been revised to use correct punctuation and grammar. The above amendments are unrelated patentability. No new matter has been added.

Applicants also amended withdrawn claims 20 and 22 to depend on and be consistent with claim 31, because

otherwise these claims depend on cancelled claims. Kindly consider the possibility of rejoinder of claims 20 and 22.

Applicants respectfully submit that the pending and examined claims define patentable subject matter warranting their allowance for the reasons discussed herein.

II. Claim Objections

On page 4, claim 26 is objected for the misspelling of the word "drug". Claim 26 has been revised to correct this spelling error. Withdrawal of the objection is therefore requested.

III. Obviousness Rejection

Claims 4-8, 23-27, and 31-36 are rejected under 35 U.S.C. §103(a) as being obvious over Yamamoto et al. (US Patent Application Publication 2003/0211166, published 13 Nov 2003) in view of Schense et al. (US Patent Application Publication 2003/0012818, 16 Jan 2003) and Shu et al. (Biomacromolecules, 2002, 2, pps. 1304-1311) for the reasons on pages 5-10. This rejection is respectfully traversed.

Yamamoto et al.

Applicants respectfully submit that the examiner's rejection seems to be the result of a misunderstanding of the disclosure of Yamamoto et al. In this regard, at page 5, lines 15-17 of the Office Action, the examiner states that "Yamamoto et al. teaches the method wherein said dilute

solution contains the crosslinking agent prior to dispersing the solution by spraying (page 4, paragraph 43 and 44)." Applicants respectfully disagree and submit that Yamamoto et al. fails to disclose or suggest that for which it is being offered.

Instead, at page 4, paragraph [0043], Yamamoto et al. actually discloses:

> The solution was treated with EDC in an aqueous phase concentration of 50 milliMolar (mM) for a period of 24 hours. The EDC treatment of the HA solution formed cross-links and thereby Increased the molecular weight of the HA and enhanced its film forming properties.

Namely, Yamamoto et al. clearly discloses that crosslinks on HA were formed by treating the HA solution with EDC for a period of 24 hours. The solution of crosslinked HA was used for preparing microspheres (see page 4, paragraph [00441] of Yamamoto et al.).

On the other hand, the method recited in independent claim 31 of the present application comprises steps b) and c), which call for dispersing the solution by spraying to form microparticulate droplets, and concentrating the solution contained in the droplets to facilitate crosslinking. Thus, in the claimed method, the crosslinking reaction of the polysaccharide derivative occurs in the microparticulate droplets produced by spraying of the reaction solution during

forming of the microspheres, as was argued in the February 9, 2009 response. This is a key technical feature of the claimed method, and it is neither shown nor made obvious, by either Yamamoto et al. or Schense et al. (as discussed further below). As neither reference shows or makes obvious this feature, no combination of the two reference together, even if such a combination were obvious, could reach the subject matter of previous claim 1 or new claim 31 which replaces claim 1.

Instead, Yamamoto et al. discloses crosslinking agent co-formulated into microspheres or a microsphere formed with crosslinked hyaluronic acid. Thus, even in light of this disclosure in Yamamoto et al. referred to in the Office Action, the above-noted feature of the claimed method is neither shown nor made obvious by Yamamoto et al. Nor is it may obvious by any combination of Yamamoto et al., Schense et al. and Shu et al. as discussed below.

Schense et al. and Shu et al.

The secondary references of Schense et al. and Shu et al. fail to remedy the noted deficiencies of Yamamoto et al.

The examiner states that "Schense et al. does not explicitly describe the gelation or matrix-forming reaction as described in page 3, paragraphs 29 and 30 to refer to the formation of a crosslinked polymer". However, Schense et al. does not include any disclosure that the crosslinked polymer can be used to form microparticles.

The method recited in claim 31 is for preparing crosslinked polysaccharide microparticles, which are suitable for administration by way of injection (see dependent claim 32). In this regard, Schense et al. states that "[d]epending on the precursor components and their concentration, gelling can occur quasi-instantaneously after mixing", and "[t]herefore, it is difficult to inject a gelled material through an injection needle" (page 6, paragraph [0075]) [emphasis added]. This teaches away from the concept of the claimed method for preparing crosslinked polysaccharide microparticles, which are suitable for administration by way of injection. It is well established that prior art references cannot be combined where a reference teaches away from their combination. *See*, M.P.E.P., Eighth Ed., Rev. 6 (September 2007) at § 2145, X, D, 2.

Accordingly, Schense et al. actually teaches away from the method of claim 31. Consequently, Applicants respectfully submit that those skilled in the art, at the time

the claimed invention was made, would not have been motivated to combine the teachings of Schense et al. with Yamamoto et al. to arrive at the claimed method, and even if they were combined, they would not have resulted in each and every feature of the method of claim 31.

Shu et al. does not help. In this regard, it should be noted that Shu et al. does not include any disclosure regarding formation of microparticles.

Thus, no combination of Yamamoto et al. and Schense et al. and Shu et al. would arrive at each and every element of the claims.

Further, it is acknowledged that Yamamoto et al. discloses formation of microparticles, at for example, paragraphs [0043] and [0044]. However, the crosslinked polymer used in Yamamoto et al. is significantly different from those disclosed in Schense et al. and Shu et al. Namely, the crosslinked polymer used in Yamamoto et al. is prepared with intact hyaluronic acid by adding EDC as a crosslinking agent to carry out esterification reaction.

The matrix disclosed in Schense et al. is formed by Michael addition reaction of multi-thiol, or mercapto groups and a conjugated unsaturated group (page 6, paragraph [0081] of Yamamoto et al.) and, thiol-modified hyaluronic acids having a thiol is disclosed in Shu et al. (page 1306, Figure

2). However, the cited references do not disclose the use of these materials to form microparticles, nor do they make obvious such use. Therefore, there is no reasonable expectation of success to use the crosslinked polymer for formation of microparticles and to combine the disclosure of Schense et al. and Shu et al. with the disclosure of Yamamoto et al. to predictably arrive at the claimed method.

Indeed, it is believed that Applicants, by way of the instant application, disclose for the first time the novel use of the hyaluronic acid derivative represented by Formula (I) or (II) for forming microparticles.

In view of the above, it is believed that no combination of Yamamoto et al., Schense et al. and Shu et al. would arrive at the method of independent claim 31. Thus, the subject matter of claim 31 and all claims dependent thereon cannot be recognized as obvious based on the combination of the cited references without impermissible use of hindsight.

For these reasons, Applicants respectfully submit the combination of Yamamoto et al., Schense et al., and Shu et al. fail to disclose or suggest each and every element of independent claim 31. Thus, claim 31 and all claims dependent thereon are believed to be novel and patentable over the combined cited references.

Therefore, the above-noted obviousness rejection is untenable and should be withdrawn.

IV. Conclusion

Having addressed all the outstanding issues, this paper is believed to be fully responsive to the Office Action. It is respectfully submitted that the claims are in condition for allowance, and favorable action thereon is requested.

If the Examiner has any comments or proposals for expediting prosecution, please contact the undersigned attorney at the telephone number below.

Respectfully submitted,

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